Perspective

Universal and Stemness-Related Tumor Antigens: Potential Use in Cancer Immunotherapy

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After a decade of cancer immunotherapy (both active and adoptive), based on the use of well-defined tumor-associated antigens (TAA), and despite the large amount of new information that has been collected both in preclinical and clinical settings, the clinical outcome of immunotherapy trials has been altogether disappointing (1, 2). Several reasons have been put forward to explain such phenomenon like tumor escape from and alterations of the immune response caused by the presence of growing tumor cells (3).

Less attention has been paid, however, to the nature of TAAs to be used in vaccine formulation. In fact, practically all the trials of immunotherapy of cancer (by and large of vaccination) conducted during the last 10 years were based on the use of TAAs encompassing normal proteins or peptides, to generate antitumor T cells mostly restricted by class I HLA (4). These TAAs are now known to be weakly immunogenic owing to different forms of tolerance to them displayed by the patients' immune system. Moreover, several of these self-TAAs have been shown to be heterogeneously expressed within the tumor mass (5) and selected against by CTLs during tumor growth allowing an immunologically unrestricted progression of the neoplasia (6, 7). Thus, the search for new, tumor-specific and immunogenic TAAs constitutively linked to the neoplastic state and, therefore, unselectable by the patient immune reactions, remains an important issue in tumor immunotherapy.

Truly tumor-specific TAAs are those expressed only by tumor cells and not by whatsoever normal cells. Such TAAs may derive (*a*) from somatic gene mutations of tumor cells resulting in new TAA epitopes recognized by the host T lymphocytes, like the unique TAAs (8, 9), or less frequently, (*b*) from alterations in splicing (10–12). Unique TAAs are now being frequently found in several human tumors, although their use in clinical trials is difficult for the time required to characterize unique TAAs at a single patient level (8, 9, 13).

Universal and Cancer Stemness-Related TAAs as Potentially More Effective Targets in Immunotherapeutic Interventions

Recently, another group of TAAs was described that include antigens overexpressed by neoplastic and fetal cells, and was weakly expressed in a phase-specific way in a few normal cells (14, 15). Such TAAs have the remarkable feature of being indispensable for tumor growth and progression. Immune responses targeting these proteins could thus result in a limited or no generation of antigen-loss variants and, therefore, they may efficiently control *in vivo* tumor growth, thus meeting the requirements for an ideal TAA set forth above. These are the so-called universal TAAs and include molecules like human telomerase reverse transcriptase (hTERT) and the inhibitor of apoptosis proteins (IAP).

An additional group of TAAs, practically unknown at the moment, includes those that might be expressed by cancer stem cells (CSC), a minor population of tumor cells which, however, shows the features of stemness (see ref. 16) and, therefore, may represent the most important target for eradicating tumor lesions even in case of immunotherapy. It is, therefore, mandatory to identify TAAs or other cell surface molecules (e.g., natural killer cell–activating receptors) of CSCs in order to assess whether they can represent a new target for the host immune system. Our prediction is that at least some of the CSC antigens will match proteins already known to serve as TAAs and expressed by embryo-fetal tissues (e.g., survivin, telomerase, cancer/testis antigens) reflecting common functions between embryonic stem cells and CSCs, i.e., multipotent differentiation, plasticity, and self-renewal. However, because these TAAs are expressed even by the majority of cancer cells of a given tumor, while CSCs encompass a small subpopulation of the tumor mass, CSCc may represent a better target if specifically enriched in cancer/testis, IAP-derived and/or mutated (unique) antigens in parallel with stem cell markers (e.g., CD44, CD133), in comparison with other tumor cells showing a more disperse concentration of such TAAs (17). Therefore, immune-mediated tumor regression should reflect a qualitative rather than a quantitative targeting aimed at eliminating a specific, minor subpopulation of tumor cells, i.e., CSC, rather than the majority of neoplastic cells. If so, this will represent a new paradigm in the immunotherapy of human tumors.

The Universal and CSC-Derived TAAs: Tissue Distribution and Immune Functions

The universal TAAs have been well-defined because of their wide distribution in human tumors of different histology, and
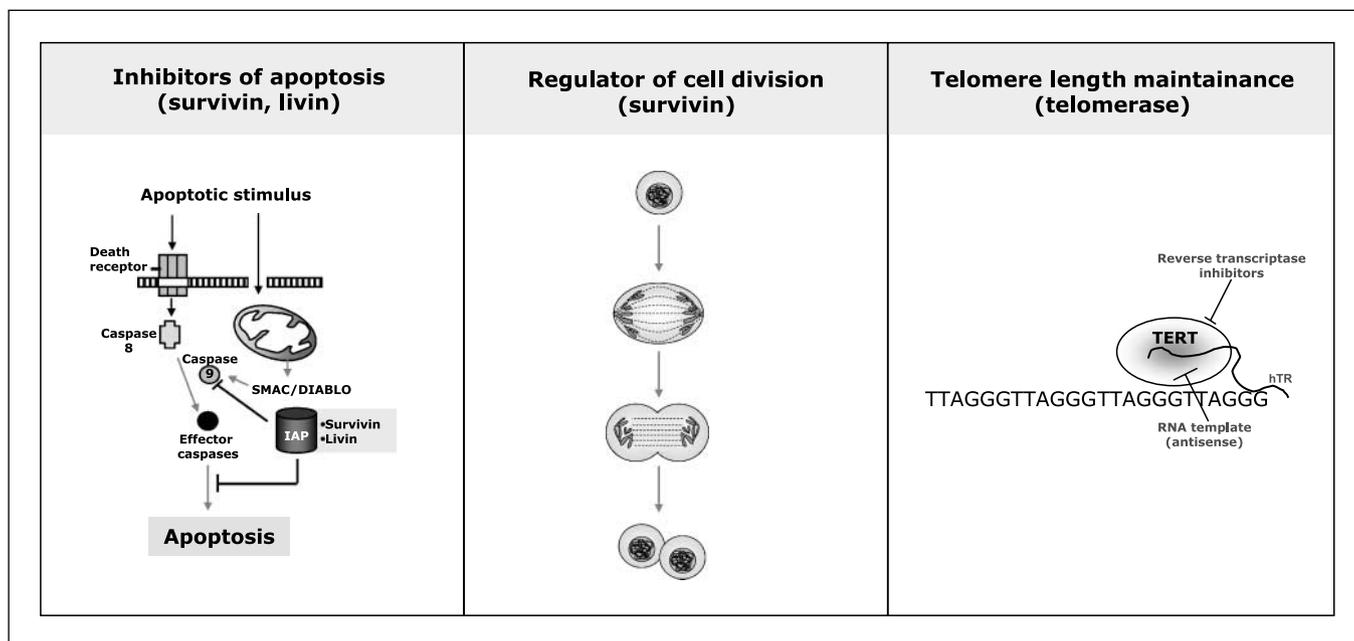
Fig. 1. Functions of survivin, livin, and telomerase in cancer cells. Survivin and livin are IAPs that interfere with the apoptotic process by blocking upstream caspase-9 activity and/or the final downstream effector step of caspase-3 and caspase-7 as well as by binding the mitochondrial protein Smac (*left*). Survivin can also favor tumor cell mitosis by localizing mostly to centrosomes and microtubules whose regular assembly is also dependent on the presence of this IAP (*middle*). Telomerase is a RNA-dependent polymerase that allows the maintenance of chromosome length and stability in tumor cells, which in turn can divide indefinitely. It includes repeated DNA sequences (TTAGGG) and associated proteins. RNA antisense and other inhibitors can block telomerase activity and allows only a limited number or divisions to tumor cells (*right*).

due to the general and fundamental functions they exert in tumor biology, i.e., that of maintaining an effective proliferation and resistance to apoptosis, thus contributing to cancer cell progression and survival (Fig. 1). CSCs should also express universal TAAs together with most cells of the tumor mass, as suggested by immunohistochemical analysis, which reveals the presence of hTERT and IAPs (e.g., survivin) in the large majority of tumor cells (15, 18). However, whether CSCs are endowed with the ability to mount IAP-derived epitopes on their HLA is being tested in ongoing studies. Preliminary findings suggest that CSCs show a variable, but in general, low expression of HLA on their surface.[3] Moreover, if the CSC target molecules are also present in normal stem cells, potential damage to normal tissues may occur. Therefore, CSC-selective elimination by immune responses should be based either on new CSC-specific targets resulting from somatic alterations/mutations of CSC genes that do not occur in normal stem cells, or in an enrichment of molecules, like the universal TAAs, that in normal stem cells cannot represent a valuable target whereas mediating a T cell cytotoxicity on neoplastic counterparts (14, 15).

Universal TAAs have recently been assessed in preclinical *in vitro* studies for their ability to generate T cell–specific immune responses (see ref. 19). Repeated stimulations of peripheral blood lymphocytes from both healthy donors and cancer patients with APCs pulsed with HLA-I restricted epitopes, entire proteins, or mRNAs encoding the antigens has made it possible to detect CD8^{+} and CD4^{+} T cell spontaneous and/or induced responses against survivin, livin, hTERT, and Bcl-2 (19–25). Importantly, these effectors recognize HLA-matched

tumor cells, which endogenously process the antigens, but not normal cells (e.g., CD34+ hematopoietic precursors, activated T and B cells; ref. 18). Moreover, *ex vivo* studies have shown a significant frequency of functional CTLs directed against hTERT among peripheral blood lymphocytes of a proportion of cancer patients as well as the presence of survivin-specific CTLs in tumor-invaded lymph nodes (26, 27). All these features make universal TAAs suitable targets for cancer immunotherapy, although a screening of single patients to analyze their capacity to mount an anti-hTERT immune response seems advisable (26).

By applying the reverse immunology approach, several peptides binding different HLA alleles have been recently identified in survivin, livin, and hTERT proteins. Some of these peptides have been shown to function as T cell epitopes being able to induce peptide-specific T cells in patients' peripheral blood mononuclear cells (see ref. 19). However, an additional crucial issue that needs to be addressed in order to consider a defined peptide as useful for a therapeutic approach is its ability to elicit T cells that can recognize the naturally processed peptide on tumor cells expressing the target protein and the appropriate HLA molecule. Although this requirement has been met for a majority of the identified peptides, for some, doubts on the efficiency of their presentation by tumor cells still remain (28, 29). An example of such a phenomenon has been reported for the hTERT peptide 540-548, which although being processed by human cells when transfected with hTERT encoding cDNA, was only marginally produced by tumor-derived proteasomes (29). In view of these observations, the functional properties of T cells elicited by immunogenic peptides should always be analyzed on a large panel of tumor cells of different histologies.

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[3] Maccalli C, Galli R, Parmiani G, unpublished results.

Clinical Trials with Universal TAAs

Although the central role of universal TAAs in malignant transformation and cancer progression and their immunogenicity have been established, only a limited number of vaccination protocols targeting IAPs have been and are being carried out (Table 1). The following is a brief summary of such clinical trials.

In a pilot study, patients with chemotherapy-resistant metastatic breast cancer or hormone-resistant prostate cancer received *ex vivo*–generated autologous dendritic cells (DC) pulsed with the HLA-A*0201–restricted hTERT I540 peptide together with keyhole limpet hemocyanin (28). Among six of the seven evaluable patients, a mixed clinical response was seen. In these patients, prevaccination and postvaccination immunohistochemical analyses of skin nodules showed a lymphoid infiltrate predominantly made of CD8$^+$ T cells, but no information on the function of these tumor-infiltrating lymphocytes was reported. A specific T cell response against hTERT was detected in the uncultured peripheral blood mononuclear cells of three patients. After 1 week of *in vitro* peptide sensitization, CD8$^+$ tetramer$^+$ T cells were seen in four patients. These CTL populations contained clones that were able to recognize and lyse hTERT expressing HLA-A*0201 cancer cells.

A peptide-based approach of immunotherapy was carried out by Parkhurst and coworkers using the same epitope emulsified in Montanide ISA51 but achieving opposite results (29). None of the 14 patients with metastatic melanoma developed a CTL response recognizing endogenously processed telomerase target cell, even though high-avidity T cell clones were obtained. Furthermore, no clinical benefits were observed in these patients.

Other hTERT-derived class I and class II epitopes given together with different adjuvants have been tested in patients with progressive and chemotherapy-unresponsive tumors. Both native and modified peptides have proved to be safe, showing their ability to induce a specific immune response without causing any sign of hematological toxicity on the blood stem cell compartment. For example, Gaudernack and coworkers treated lung and pancreatic cancer patients with HR2822 (540-548) and GV1001 (611-626) hTERT-derived epitopes (30, 31). The latter is a promiscuous HLA class II epitope that has been shown to induce a strong CD4$^+$ T cell response able to generate and sustain a CTL response. The immunologic responder patients showed a tendency for a prolonged survival as compared with historical controls. This seems to be important considering the aggressiveness and the immune-suppressive activity that characterizes these tumors.

In the effort to overcome the problems of altered antigen processing, hTERT mRNA was used to transfect metastatic prostate cancer–derived DCs (22). In a subgroup of patients, a chimeric transcript made of the lysosomal-associated membrane antigen-1 was fused to the target antigen, thus improving the generation of CD4$^+$ T response. Although no clinical benefits were achieved in either group, transient and short-lasting effects on prostate-specific antigen doubling times were obtained in some patients.

In the attempt to develop a polyvalent vaccine targeting both patient-specific tumor and stromal targets, total RNA derived from renal tumor tissue was used to transfect patients' autologous DCs (32). Although no assessment of the therapeutic effect could be made, a strong immunologic response against hTERT was elicited.

Clinical experience on the use of survivin in tumor vaccination trials is limited to few studies (19), despite the development of a spontaneous immune response to such an antigen, which seems to be quite common in patients with cancer. A modified HLA-A*0201 epitope of survivin (96-104, 2M) has been used to vaccinate stage IV melanoma patients with DC as adjuvant (33). Four out of five patients mounted a specific antisurvivin immune response detected both in the peripheral blood and in metastatic lesions showing the ability of the vaccine-induced CD8$^+$ T cell population to home into peripheral tumor tissues. At the same time, these patients experienced an unexpected long survival.

In a phase I trial, eight patients with hormone-refractory prostate cancer received autologous DCs pulsed with HLA-A*0201–restricted epitopes derived from prostate cancer–associated antigens and survivin (95-104; ref. 34). In this trial, the strongest reduction of prostate-specific antigen plasma levels was observed in the four patients (one with partial remission and three with stable disease) developing specific CD8$^+$ T cell–mediated immune response, only two of whom, however, directed against the survivin epitope.

In our centers (Istituto Nazionale Tumori, San Raffaele Scientific Institute), clinical trials involving vaccination with

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Table 1. Clinical trials involving the use of universal TAAs

Antigen	Tumor	No. of patients	Immune responders	Clinical outcome	Reference
hTERT$_{540-548}$	Breast/prostate	7	4	6/7*	(28)
hTERT$_{540-548}$ + Montanide	Melanoma	14	0	0	(29)
hTERT$_{611-626}$ + GM-CSF	Pancreas	48	24/38	ND	(31)
hTERT$_{540-548}$ + hTERT$_{611-626}$ + GM-CSF	NSCLC	26	2/24 (for 540-548) 13/24 (for 611-626)	1 CR	(30)
hTERT mRNA loaded DCs	Prostate	20	19	NE	(32)
Survivin$_{96-104}$ pulsed DCs	Melanoma	5	4	>OS †	(33)
Survivin$_{95-104}$ pulsed DCs	Prostate	8	4	1 PR, 3 SD	(34)

Abbreviations: ND, not determined; NSCLC, non–small cell lung cancer; CR, complete remission; NE, not evaluable; GM-CSF, granulocyte macrophage colony-stimulating factor; OS, overall survival; PR, partial remission; SD, stable disease.
* Mixed responses only.
† Increased long-term survival without statistical assessment.

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peptides derived from survivin are presently ongoing. These trials are based on the administration of multiple HLA-A*0201–restricted peptides derived from differentiation antigens and cyclophosphamide aimed at reducing the *in vivo* effect of regulatory T cells. This approach is under evaluation in early stage melanoma, prostate cancer patients with biochemical failure after conventional treatments (receiving PSMA and survivin-derived peptides), and in locally recurrent rectal carcinoma (with carcinoembryonic antigen and survivin-derived epitopes). Preliminary immunologic analysis shows that a significant boost of T cells specific for all the administered peptides, including survivin, could be detected in both PBLs and in draining lymph nodes.[4]

Altogether, these early clinical trials have enrolled a limited number of patients and are too heterogeneous in terms of vaccine formulation and tumor targets to allow any meaningful conclusion on the clinical efficacy of immunizations based on universal TAAs. Further results of ongoing phase II studies with a larger number of patients are eagerly awaited in order to assess the importance of this approach for cancer therapy.

Perspectives

From the studies on universal TAAs, we have learned that such antigens are, more than any other TAAs, frequently expressed in many different human tumors and, therefore, they apparently provide the most common, neoplasia-related and easily identifiable immune target. Upon closer examination, however, it remains to be established whether hTERT is more immunogenic for T cells of cancer patients as compared with other TAAs obtained from the same tumor as suggested by Su and coworkers in renal cell carcinoma patients vaccinated with tumor RNA pulsed DCs (22). In fact, a different study found that the frequency of HLA-A2–restricted T cell precursors against hTERT peptide was similar in cancer patients and in normal donors (35).

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[4] Rivoltini L, Castelli C, Parmiani G, unpublished results.

As for survivin, cancer patients were shown to have spontaneous T cell responses against survivin peptides (27) and we have also shown that anti-survivin T cell precursors are detectable in cancer patients but not in normal individuals (24); importantly, such T cells were found to recognize tumor cells expressing survivin. These findings suggest that survivin may be strongly immunogenic in at least a fraction of patients.

Whether these antigens might also actually represent a significant target for CSCs is unknown at the moment. However, the study of the immunogenic potential of universal TAAs is worth pursuing because it may pave the way for *in vitro* and *in vivo* characterization of similar, if not identical, TAAs expressed by CSCs; thus allowing their use as targets in future trials of cancer immunotherapy. The presence of CSCs in the tumor mass may change the whole paradigm of cancer immunotherapy with the need for preparing T and/or natural killer cell effectors and/or antibodies able to recognize and preferentially destroy the small CSC subpopulation, rather than a huge number of lymphocyte effectors aimed at targeting as many tumor cells as possible. Because the markers (antigens?) which have thus far been reported to characterize different types of CSC (e.g., ESA, CD44, CD133; refs. 16, 36–47) seem to be normal molecules involved in the process of cell adhesion and migration, it is likely that such molecules may be more easily targeted by antibodies than by antigen-specific T cells. In fact, an antibody against CD44 has recently been shown to eradicate xenografted human acute myelogenous leukemia stem cells, possibly by interfering with the CSC-supporting microenvironment (48). The anti-CSC function of T cells, however, cannot be completely discarded. In fact, one of CSC's most common markers, ESA (Ep-CAM; refs. 16, 39), has been shown to contain epitopes that can be recognized by class I HLA–restricted T cells (49), and which has been used to vaccinate colorectal cancer patients, although with limited success (50). In this context, vaccines containing T cell–defined universal and CSC TAAs and their combination with antibodies targeting the cell surface molecules expressed by CSCs (e.g., CD44) may be much more effective than those including self-TAAs previously used in cancer vaccination.

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